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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/467,901	12/21/1999	JOOST VAN NEERVEN	02405.0190	2936

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EXAMINER	
DO, PENSEE T	12

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/467,901	NEERVEN, JOOST VAN	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on September 4, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/467,901 is acceptable and a CPA has been established. An action on the CPA follows.

Information Disclosure Statement

The information disclosure statement filed on August 29, 2001 has been acknowledged and entered as paper no.10.

Amendment Entry & Claim Status

The amendment filed on November 30, 2001 has been acknowledged and entered. Claims 1-22 are pending.

Claim Rejections - 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 7, 17-19 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. A second separation step is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining

whether a disclosure would require undue experimentation include (1) nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention: - the instant invention is directed to a method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising adding the sample to a ligand and then adding a receptor bound to a carrier to the mixture; separation; adding a label; detection.

The state of the art: - the prior art a method teaches that after adding a label, a second separation step is required to separate all the non-complexed labels.

The predictability or lack thereof in the art:- in view of the teachings in the prior art that show or suggests a second separation step after adding the labels, detection is impossible if a second separation is not carried out because there would be non-complexed labels in the mixture.

The amount of direction or guidance present: - the instant specification fails to provide guidance on how to detect/measure IgE without the second separation step after adding a label.

The presence or absence of working examples:- there is no examples in the specification that show that detection can be carried out without the second separation step.

The quantity of experimentation necessary: - it would require an undue amount of experimentation for a skilled artisan to make and use the invention as claimed.

The relative skill of those in the art: The level of skill in the art is high.

The breadth of the claims:- the claimed method is directed to detection and/or quantification of an IgE antibody specific to a ligand in a liquid sample suspected to contain the IgE antibody.

The claims fail to recite an essential or critical step which is the second separation step after adding a label to the mixture. Without the second separation step, the non-complexed labels are present and thus detection of the labeled-bound IgE is impossible.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10-16, 17-19, 21, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is missing a step of adding a label. The label in step (d) has not been introduced in any of the previous step. Thus, it is unclear when the label is added.

Claims 10-16 are rejected because they depend from claim 1.

Claim 17 is confusing in step (d). In view of the separation step (c), why would the labeled antibodies be specific to the complexes formed in

steps (a) or (b)? Those complexes should be gone or complexed to the carrier.

Claims 18-19 are rejected because they depend from claim 17.

Claims 21 & 22 are unclear of what the purpose of the method is. The preamble recites a method of monitoring and evaluating the immunological status of a subject while the body recites step of determining amount of the carrier-bound IgE containing complexes. What does this step have anything to do with monitoring and evaluating the immunological status of a subject?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5, 21-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Frank et al. (US 5,945,294).

Frank et al. teaches an assay in which the biological sample is applied to the sample receiving zone which includes a portion of the support structure. The labeling zone receives the sample from the sample receiving zone, which is directly downstream by the flow path. The labeling zone comprises the labeling reagent that binds to IgE (sample). A preferred labeling reagent is an antigen (ligand) conjugated, either directly or through a linker, to a plastic bead substrate, such as latex bead. Downstream to the labeling zone is a capture zone, which receives labeling reagent from the labeling zone. The capture zone contains the capture reagent, in this case Fc∈R molecule (IgE receptor) that immobilizes the IgE complexes to the antigen in the capture zone. The capture reagent is fixed to the support structure (carrier). The labeling reagent accumulates in the capture zone and the accumulation is detected visually or by optical detection device (see col. 13, line 54-col. 14, line 8). Frank et al. teach a method for detecting IgE comprising Frank also discloses that the Fc0R:IgE complex is detected by contacting the complex with a reagent that selectively binds to an IgE antibody (anti-IgE ligand). Examples of such anti-IgE ligand includes anti-isotype antibody (an antibody that binds to the constant region of an IgE to be detected) the anti-IgE ligands are labeled with biotin, horseradish peroxidase or fluorescein. In another embodiment, a complex can be formed and detected in solution. In another embodiment, a complex can be formed in which one or more members of the complex are immobilized on a substrate. Separation is performed when the complexes are captured at the capture zone and the rest of the solvent flows to the absorbent downstream from the capture zone (see col. 10, lines 5-61). Regarding claims 21 and 22, although the preamble

recites a method for monitoring and evaluating the immunological status of a subject, the method steps are the same as those in claims 1-4. Thus, Frank reads on the method steps of claims 21-22.

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-5, 8-16, 21, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) further in view of Johnson et al. (US 6,034,066) and Frank et al. (US 6,060,326).

Johansen et al. teach a method of detecting an antibody in a sample using a labeling compound and comprising the steps of mixing the ligand antigen, antibody or hapten bound to biotin with the sample; an antibody is directed against the antibody to be detected bound to a paramagnetic particles; and a chemiluminescent acridinium compound bound to avidin or streptavidin to form a solid phase complex; separating the solid phase from the liquid phase; and analyzing the separated solid phase for the presence of chemiluminescent complex. There are several embodiments. In one embodiment, the method comprises the following steps: mixing the ligand antigen, antibody or hapten bound to biotin or a functional derivative thereof with the samole and

the antibody directed against the antibody to be detected bound to paramagnetic particles to form a first solid phase complex; adding a chemiluminescent acridinium compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex; magnetically separating the solid phase from the liquid phase; initiating the chemiluminescent reaction, and analyzing the separated solid phase for the presence of the chemiluminescent complex. Johansen et al. also teaches the method for the quantification of specific antibodies, such as immunoglobulins, wherein a truly parallel reference immunoassay using an identical protocol as a reference. The method comprises measuring the concentration and/or the relative contents of a specific antibody in a liquid sample, wherein the measured light emission of a separated solid phase comprising a captured specific antibody coupled to a chemiluminescent label is compared with the measured light emission obtained in a parallel reference immunoassay wherein the total contents of the class of antibodies in the sample to which said specific antibody belongs is measured. The method comprising the steps of mixing a ligand antigen, hapten towards which the specific antibody to be measured is directly bound to biotin or a functional derivative thereof; an antibody directed against the constant portion of the antibody to be measured bound to paramagnetic particles and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof with the sample to form a first solid phase from the liquid phase; magnetically separating the first solid phase from the liquid phase; initiating a chemiluminescent reaction and measuring the light emission of the separated first solid phase; mixing a ligand antibody directed against the class of

antibodies to be measured bound to biotin or a functional derivative thereof ; an antibody directed against the constant portion of the class of antibodies to be measured bound to paramagnetic particles ; and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof wherein the term total shall mean the entire amount of the designated class of immunoglobulins (e.g. IgA, IgE, etc.) With the sample to form a second solid phase complex, magnetically separate the second solid phase form the liquid phase; initiating the light emission of the separated first solid phase with that of the separated second solid phase. The specific antibody to be measured in the sample is preferably a specific immunoglobulin selected from the group consisting of IgA, IgD, IgE, IgG, IgM and subclasses thereof. (See col. 3, line 30-col. 5, line 45).

However, Johansen et al. fails to teach using an IgE receptor to bind IgE antibody/ligand complexes and a method of quantification of IgE wherein the IgE to be detected is quantified using both CD23 alone to obtain a first measurement and using FcORII alone to obtain a second measurement.

Johnson et al. teach multiple important roles of CD23 in the regulation of immune responses, particularly the regulation of IgE responses. Among these roles, CD23 acts as a cellular receptor for IgE and is found in various cell types including B cells. (See col. 1, line 31-col. 2, line 64).

Frank et al. teach detecting IgE antibodies using a human Fc epsilon receptor FcOR. (See col. 1, line 45-col. 2, line 10).

It would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson et al. and Frank et al. to measure IgE according to the method of Johansen et al. since both of these receptors, CD23 and FcϴR, are specific to IgE antibody and because FcϴR and CD23 can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. (See Frank et al. Col. 1, lines 19-34). Regarding claim 16, wherein the number of ligand molecules is between 100% and 200 % of the number of IgE molecules to be detected, it would have been obvious to one of ordinary skills in the art to use enough ligand molecules to optimize binding of all the IgE molecules to be detected. In order to detect 100% of the IgE present in the sample, at least 100% of ligand molecules must be present to bind all the IgE present in the sample.

Response to Arguments

The arguments filed on November 30, 2002 has been considered but found not persuasive.

Regarding the 102(e) rejection by Johansen et al., the arguments are moot in view of the new 103(a) rejection.

Regarding, the 102(e) rejection by Frank et al., Applicants argue that Frank used an antigen (ligand) that was fixed to a plastic bead. The instant invention uses a free, dissolved ligand. Thus, Frank does not disclose all the claimed invention's elements and cannot anticipate claims 1, 17-19.

Frank teaches that the ligand is bound to a plastic bead, and the plastic bead is also labeled with a colorimetric marker. In operation, when the sample contacts the

labeled ligand bound plastic bead in the labeling zone, the labeled ligand bound plastic bead dissolves and moves freely along the flow path to the capture region wherein the IgE (analyte to be detected in the sample)-labeled ligand bound plastic bead is captured by an IgE receptor - Fc∈R molecule. The capturing step is also the separation step of complexes from the non-complexes. Thus, Frank meets the requirement of the claimed invention of a free-dissolved ligand. Since the claims contain opening language, the beads can be interpreted as part of the label.

Claims 6,7, 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) in view of Frank et al. (US 6,060,326) further in view of Arnold, Jr. et al. (US 6,004,745).

Johansen et al. and Frank et al. have been discussed above.

However, Johansen and Frank fail to teach adding label after a first separation step and a second separation to separate the non-complexed labels.

Arnold, Jr. discusses in the background section that a typical sandwich assay involve incubating an immobilized antibody (IgE receptor) with a test medium (sample). Antigens, if in the medium, will bind to the antibody. After incubation, unbound antigen is removed in a separation step. After a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes sandwiched between the immobilized antibody and the labeled antibody. After a second separation step, the amount of labeled antibody can be determined as a measure of the antigen in the medium. (see col. 1, lines 55-66).

It would have been obvious to one of ordinary skill in the art to add the label molecule after a first separation step and then separating the non-complexed labels as discussed in Arnold, Jr. using the reagents in the method of Johansen modified by Frank because such second separation steps, although time consuming, increases the sensitivity of the assay results. Furthermore, since the non-complexed immobilized antibody and the non-complexed labels are separated one at a time, cross-reactivity between the label and the immobilized antibody/reagent is eliminated.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is (703) 308-4398. The examiner can normally be reached on Mon-Fri. from 7 a.m. to 3 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
3/27/03

Pensee T. Do
Patent Examiner
March 21, 2003